REMARKS

Claims 1-12 are pending in the present application. Claims 2-8 and 10-12 have been canceled, Claims 1 and 9 have been amended, and Claims 13-26 have been added, leaving Claims 1, 9, and 13-26 for consideration upon entry of the present Amendment.

Support for the amendment to claims 1 and 9 can be found in the specification on page 28, line 15 to page 29, line 4.

Support for new claims 13, 16, 17 and 20 can be found in the specification on page 28, line 15 to page 29, line 4.

Support for new claims 14, 15, 18 and 19 can be found in the specification on page 29, lines 5-14.

Support for new claims 21-26 can be found at least in examples 15-17.

No new matter has been introduced by these amendments. Reconsideration and allowance of the claims is respectfully requested in view of the above amendments and the following remarks.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 4, and 9 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in relevant art that the inventors, at the time the applications was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

In particular, the Examiner alleges "The scope of potential inhibitors is so vast as to include any type of antagonist compound that may antagonize EDG-1 signal transduction. This means that any component of any EDG-1 signal transduction cascade, upstream or downstream, may be a potential target of the antagonist used in the instantly claimed methods". (paper 2005317, page 3)

Claims 1 and 9 have been amended to specify that the antagonist inhibits phosphorylation of T^{236} of the EDG-1 receptor. Thus, the claims are not so broad as to encompass all inhibitors, but only those inhibitors that inhibit a specific phosphorylation of

the EDG-1 receptor. In an important aspect of the invention, the inventors have clearly shown that SPP induces phosphorylation of Akt through a Gi/PI-3-kinase pathway using Wortmannin and LY294002 as PI-3 kinase inhibitors. SPP was further shown to stimulate the association of Akt and EDG-1 and to stimulate phosphorylation of EDG-1 at T^{236}. The PI-3 kinase inhibitor LY294002, for example, suppressed the SPP-induced phosphorylation of EDG-1. Thus, antagonists that inhibit phosphorylation of T^{236} of the EDG-1 receptor inhibit EDG-1 activation and thus will inhibit EDG-1-mediated angiogenesis.

In addition, new claims 13 and 17 specify that the antagonist inhibits the PI-3 kinase. The Akt kinase is phosphorylated through the Gi/PI-3-kinase pathway, thus inhibiting the PI-3 kinase results in decreased phosphorylation of the Akt kinase which leads to decreased phosphorylation of the EDG-1 receptor. The PI-3 kinase inhibitor LY294002, for example, suppressed the SPP-induced phosphorylation of EDG-1.

New claims 14 and 18 specify that the antagonist inhibits chemotaxis of a cell expressing the EDG-1 receptor. Claims 15 and 19 specify that the antagonists inhibit the production of cortical actin structures. Because Akt is a known intermediate in chemotaxis, the role of Akt activity in SPP-induced responses in HUVEC cells was determined. SSP-induced cortical actin structures were inhibited by the PI-3 kinase inhibitors Wortmannin and LY294002. The role of Akt signaling in cell migration was also studied in CHO cells overexpressing the EDG-1 and EDG-3 receptors. SSP induced cell migration in CHO cells expressing EDG-1. Thus, the inventors have clearly shown that the Akt signaling pathway involved in the formation of EDG-1-induced cortical actin structures.

New claims 16 and 20 specify that the antagonist is a small molecule. The claimed method is exemplified using Wortmannin and LY294002, both small molecule antagonists.

The Examiner goes on to state that "The instant specification discloses two antisense oligonucleotides targeted to human EDG-1 which inhibits EDG-1 in cell culture...The specification as filed does not provide the actual structure of any other EDG-1 signal transduction, for example". (paper 2005317, page 3) Applicants disagree with the Examiner's characterization of the specification.

As described above, in addition to antisense oligonucleotides, the inventors have employed the PI-3 kinase inhibitors Wortmannin and LY294002 to inhibit EDG-1 signal transduction. Wortmannin and LY294002 inhibit phosphorylation of the Akt kinase which in turn inhibits phosphorylation of T^{236} of the EDG-1 receptor. The inventors have also shown that inhibition of phosphorylation of T^{236} of the EDG-1 receptor inhibits chemotaxis by inhibiting the production of cortical actin fibers. Thus, inhibitors of Akt kinase or PI-3 kinase would be expected to inhibit phosphorylation of T^{236} of the EDG-1 receptor. It is inhibiting angiogenesis by inhibiting phosphorylation of T^{236} of the EDG-1 receptor that is presently claimed. The antisense oligonucleotides described by the Examiner do not function in this manner.

Applicants believe that the claims as drafted may have been confusing to the Examiner. Claim 4 as filed has been cancelled because an antagonist that inhibits phosphorylation of T^{236} of the EDG-1 receptor can be an Akt kinase inhibitor.

The Examiner then goes on to state "The specification fails to provide a description of any particular structure or structures that would be shared with the genus of antagonist such that one in the art would be apprised of the structure which corresponds to the function of antagonizing EDG-1 signal transduction". (paper 2005317, page 4) The Examiner specifically points to several cases including University of Rochester v. G.D. Searle and Co., wherein it is stated "[t]he claimed method depends upon finding a compound that selectively inhibits PHGS-2 activity. Without such a compound, it is impossible to practice the claimed method of treatment".

In the University of Rochester v. G.D. Searle and Co. case, no compounds which inhibit PHGS-2 activity had been identified at the time of filing. This is in contrast to the present case in which Applicants have shown two compounds, namely Wortmannin and LY294002, the function in the claimed method. Applicants also point out that Wortmannin and LY294002 have different structures, thus the inventors have shown that two very different small molecule inhibitors function in the claimed methods.

In the present application, compounds have been claimed by their function as

inhibitors of phosphorylation of T^{236} of the EDG-1 receptor. Suitable compounds include, for example, inhibitors of PI-3 kinase exemplified by Wortmannin and LY294002, two structurally distinct compounds. Suitable assays for identifying inhibitors that will function in the claimed methods are described in the present application and include, for example:

1. HUVEC can be treated with ^{32}P-orthophosphate and the effect of test compounds on the level of phosphorylation of EDG-1 determined. The labeled EDG-1 can be immunoprecipitated with an anti-EDG-1 antibody and the label detected by autoradiography. (Example 15)

2. EDG-1-Akt association can be determined by attaching an anti-EDG-1 antibody to protein-A beads and using the beads to isolate EDG-1-Akt complexes. (Example 16)

3. HUVEC cells expressing wild-type Akt, dominant-negative Akt, and constitutively active Akt (myr-Akt) can be assayed for the production of cortical actin structures. (Example 17)

4. CHO cells expressing EDG-1 can be assayed for cell migration. (Example 16)

Thus, the inventors have shown two examples of antagonists that function in the claimed methods and have given several examples of assays that may be employed to identify additional antagonists.

The Examiner also states "The specification has not shown any compounds that have been shown to inhibit angiogenesis in an animal or which has been shown to inhibit EDG-1 signal transduction in vivo". (paper 2005317, page 4) First, Applicants point out that HUVEC cells are an accepted in vitro model for the study of angiogenesis. One of skill in the art would recognize that studies performed in HUVEC cells are indicative of results obtained from in vivo studies. In support of this idea, Applicants respectfully point the Examiner to Example 21 in which a Matrigel model of in vivo angiogenesis in nude mice was employed. In this study, a T236AEDG-1 virus (that is, a mutation of T^{236} of the EDG-1 receptor that renders it incapable of phosphorylation) inhibited invasion/migration of neovessels into the Matrigel plugs. In combination with the data in HUVEC cells, one of ordinary skill in the art would appreciate the importance of phosphorylation of T^{236} of the

EDG-1 receptor on angiogenesis, and that inhibition of phosphorylation in vitro or in vivo would be expected to inhibit angiogenesis.

For at least the foregoing reasons, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, are rejected.

Claims 1, 4 and 9 also stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claims allegedly contain subject matter which was not described in the specification in a way as to enable one skilled in the art to which it pertains to make and/or use the invention.

In particular, the Examiner points to two antisense oligonucleotides and describes the unpredictability of the art regarding antisense oligonucleotides. Applicants respectfully point out that the claims are directed to wherein the antagonist inhibits phosphorylation of T^{236} of the EDG-1 receptor. Thus, the claims do not encompass the antisense oligonucleotides referred to by the Examiner, but instead encompass compounds such as Wortmannin and LY294002 which inhibit phosphorylation of T^{236} of the EDG-1 receptor. Thus, the unpredictability of the antisense arts is a moot point.

The Examiner then goes on to allege that the quantity of experimentation required to determine potential antagonists is undue.

Applicants respectfully point out that the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985).

Methods and tools for screening of drug candidates are well-known in the art. As described above, Applicants have identified 4 assays which can be adapted by one of skill in for identifying compounds that will function in the claimed methods. Applicants submit that

one of skill in the art could apply such tools to screen for compounds that antagonize EDG-1 signal transduction, such as compounds that inhibit PI-3 kinase activity. Thus, while some experimentation may be required, such experimentation is within the skill of one of ordinary skill in the art given the tools provided in the present application and those tools commenly used in the art.

For at least the foregoing reasons, reconsideration and withdrawal of the rejections under 35 U.S.C. 112, first paragraph, are requested.

New claims 21-26

New claims 21-26 are directed to methods of screening compounds for inhibition of angiogenesis. Applicants submit that such claims present similar issues to the method of treatment claims under examination and do not present an undue burden for examination.

It is believed that the foregoing amendments and remarks fully comply with the Office Action and that the claims herein should now be allowable to Applicants. Accordingly, reconsideration and allowance is requested.

If there are any additional charges with respect to this Amendment or otherwise, please charge them to Deposit Account No. 06-1130 maintained by Cantor Colburn LLP.

Respectfully submitted,

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